CABERGOLINE - cabergoline tablet
Par Pharmaceutical, Inc.

DESCRIPTION

Cabergoline Tablets contain cabergoline, a dopamine receptor agonist. The chemical name for cabergoline is 1-[(6-allylergolin-8ß-yl)-carbonyl]-1-[3-(dimethylamino)propyl]-3-ethylurea. Its molecular formula is $C_{26}H_{37}N_5O_2$, and its molecular weight is 451.62. The structural formula is as follows: 

Cabergoline is a white powder soluble in ethyl alcohol, chloroform, and N, N-dimethylformamide (DMF); slightly soluble in 0.1N hydrochloric acid; very slightly soluble in n-hexane; and insoluble in water.
Each tablet, for oral administration, contains 0.5 mg of cabergoline. Inactive ingredients consist of citric acid, croscarmellose sodium, magnesium stearate and microcrystalline cellulose.

CLINICAL PHARMACOLOGY

Mechanism of Action: The secretion of prolactin by the anterior pituitary is mainly under hypothalmic inhibitory control, likely exerted through release of dopamine by tuberoinfundibular neurons. Cabergoline is a long-acting dopamine receptor agonist with a high affinity for D_2 receptors. Results of *in vitro* studies demonstrate that cabergoline exerts a direct inhibitory effect on the secretion of prolactin by rat pituitary lactotrophs. Cabergoline decreased serum prolactin levels in reserpinized rats. Receptor-binding studies indicate that cabergoline has low affinity for dopamine D_1, α_1- and α_2-adrenergic, and 5-HT_1- and 5-HT_2-serotonin receptors.
Clinical Studies: The prolactin-lowering efficacy of cabergoline was demonstrated in hyperprolactinemic women in two randomized, double-blind, comparative studies, one with placebo and the other with bromocriptine. In the placebo-controlled study (placebo n=20; cabergoline n=168), cabergoline produced a dose-related decrease in serum prolactin levels with prolactin normalized after 4 weeks of treatment in 29%, 76%, 74% and 95% of the patients receiving 0.125, 0.5, 0.75, and 1 mg twice weekly, respectively.
In the 8-week, double-blind period of the comparative trial with bromocriptine (cabergoline n=223; bromocriptine n=236 in the intent-to-treat analysis), prolactin was normalized in 77% of the patients treated with cabergoline at 0.5 mg twice weekly compared with 59% of those treated with bromocriptine at 2.5 mg twice daily. Restoration of menses occurred in 77% of the women treated with cabergoline, compared with 70% of those treated with bromocriptine. Among patients with galactorrhea, this symptom disappeared in 73% of those treated with cabergoline compared with 56% of those treated with bromocriptine.

Pharmacokinetics

Absorption: Following single oral doses of 0.5 mg to 1.5 mg given to 12 healthy adult volunteers, mean peak plasma levels of 30 to 70 picograms (pg)/mL of cabergoline were observed within 2 to 3 hours. Over the 0.5 to 7 mg dose range, cabergoline plasma levels appeared to be dose-proportional in 12 healthy adult volunteers and nine adult parkinsonian patients. A repeat-dose study in 12 healthy volunteers suggests that steady-state levels following a once-weekly dosing schedule are expected to be twofold to threefold higher than after a single dose. The absolute bioavailability of cabergoline is unknown. A significant fraction of the administered dose undergoes a first-pass effect. The elimination half-life of cabergoline estimated from urinary data of 12 healthy subjects ranged between 63 to 69 hours. The prolonged prolactin-lowering effect of cabergoline may be related to its slow elimination and long half-life.
Distribution: In animals, based on total radioactivity, cabergoline (and/or its metabolites) has shown extensive tissue distribution. Radioactivity in the pituitary exceeded that in plasma by >100-fold and was eliminated with a half-life of approximately 60 hours. This finding is consistent with the long-lasting prolactin-lowering effect of the drug. Whole body autoradiography studies in pregnant rats showed no fetal uptake but high levels in the uterine wall. Significant radioactivity (parent plus metabolites) detected in the milk of lactating rats suggests a potential for exposure to nursing infants. The drug is extensively distributed throughout the body. Cabergoline is moderately bound (40% to 42%) to human plasma proteins in a concentration-independent manner. Concomitant dosing of highly protein-bound drugs is unlikely to affect its disposition.
Metabolism: In both animals and humans, cabergoline is extensively metabolized, predominately via hydrolysis of the acylurea bond or the urea moiety. Cytochrome P-450 mediated metabolism appears to be minimal. Cabergoline does not cause enzyme induction and/or inhibition in the rat. Hydrolysis of the acylurea or urea moiety abolishes the prolactin-lowering effect of cabergoline, and major metabolites identified thus far do not contribute to the therapeutic effect.
Excretion: After oral dosing of radioactive cabergoline to five healthy volunteers, approximately 22% and 60% of the dose was excreted within 20 days in the urine and feces, respectively. Less than 4% of the dose was excreted unchanged in the urine. Nonrenal and renal clearances for cabergoline are about 3.2 L/min and 0.08 L/min, respectively. Urinary excretion in hyperprolactinemic patients was similar.

Special Populations

Renal Insufficiency: The pharmacokinetics of cabergoline were not altered in 12 patients with moderate-to severe renal insufficiency as assessed by creatinine clearance.

Hepatic Insufficiency: In 12 patients with mild-to-moderate hepatic dysfunction (Child-Pugh score ≤10), no effect on mean cabergoline C_{max} or area under the plasma concentration curve (AUC) was observed. However, patients with severe insufficiency (Child-Pugh score >10) show a substantial increase in the mean cabergoline C_{max} and AUC, and thus necessitate caution.
Elderly: Effect of age on the pharmacokinetics of cabergoline has not been studied.

Food-Drug Interaction
In 12 healthy adult volunteers, food did not alter cabergoline kinetics.

Pharmacodynamics
Dose response with inhibition of plasma prolactin, onset of maximal effect, and duration of effect has been documented following single cabergoline doses to healthy volunteers (0.05 to 1.5 mg) and hyperprolactinemic patients (0.3 to 1 mg). In volunteers, prolactin inhibition was evident at doses >0.2 mg, while doses ≥0.5 mg caused maximal suppression in most subjects. Higher doses produce prolactin suppression in a greater proportion of subjects and with an earlier onset and longer duration of action. In 12 healthy volunteers, 0.5, 1 and 1.5 mg doses resulted in complete prolactin inhibition, with a maximum effect within 3 hours in 92% to 100% of subjects after the 1 and 1.5 mg doses compared with 50% of subjects after the 0.5 mg dose.
In hyperprolactinemic patients (n=51), the maximal prolactin decrease after a 0.6 mg single dose of cabergoline was comparable to 2.5 mg bromocriptine; however, the duration of effect was markedly longer (14 days vs 24 hours). The time to maximal effect was shorter for bromocriptine than cabergoline (6 hours vs 48 hours).
In 72 healthy volunteers, single or multiple doses (up to 2 mg) of cabergoline resulted in selective inhibition of prolactin with no apparent effect on other anterior pituitary hormones (GH, FSH, LH, ACTH, and TSH) or cortisol.

INDICATIONS AND USAGE
Cabergoline Tablets are indicated for the treatment of hyperprolactinemic disorders, either idiopathic or due to pituitary adenomas.

CONTRAINDICATIONS
Cabergoline Tablets are contraindicated in patients with
- Uncontrolled hypertension or known hypersensitivity to ergot derivatives.

- History of pulmonary, pericardial, cardiac valvular, or retroperitoneal fibrotic disorders. (See **PRECAUTIONS, Fibrosis**).

WARNINGS
Valvulopathy: Post marketing cases of cardiac valvulopathy have been reported in patients receiving cabergoline. These cases have generally occurred during long-term administration of high doses of cabergoline (>2mg/day) used for the treatment of Parkinson's disease. Rare cases have been reported associated with short-term treatment (<6 months) or in patients receiving lower doses for the treatment of hyperprolactinemia.
Physicians should use the lowest effective dose of cabergoline for the treatment of hyperprolactinemia and should periodically reassess the need for continuing therapy with cabergoline. In addition, patients receiving long term treatment with cabergoline should undergo periodic reassessment of their cardiac status, and echocardiography should be considered. Any patient who develops signs or symptoms of cardiac disease, including dyspnea, edema, congestive heart failure, or a new cardiac murmur, while being treated with cabergoline should be evaluated for possible valvulopathy.
Cabergoline should be used with caution in patients who have hemodynamically significant valvular disease or have been exposed to other medications associated with valvulopathy.
Pregnancy: Dopamine agonists in general should not be used in patients with pregnancy-induced hypertension, for example, preeclampsia eclampsia, and post partum hypertension, unless the potential benefit is judged to outweigh the possible risk.

PRECAUTIONS
General: Initial doses higher than 1 mg may produce orthostatic hypotension. Care should be exercised when administering cabergoline with other medications known to lower blood pressure.
Postpartum Lactation Inhibition or Suppression: Cabergoline is not indicated for the inhibition or suppression of physiologic lactation. Use of bromocriptine, another dopamine agonist for this purpose, has been associated with cases of hypertension, stroke, and seizures.
Hepatic Impairment: Since cabergoline is extensively metabolized by the liver, caution should be used, and careful monitoring exercised, when administering cabergoline to patients with hepatic impairment.
Fibrosis: As with other ergot derivatives, pleural effusion/pulmonary fibrosis and valvulopathy have been reported following long-term administration of cabergoline. Some reports were in patients previously treated with ergotinic dopamine agonists. Therefore, CABERGOLINE should be used with caution in patients with a history of, or current signs and/or clinical symptoms of, respiratory or cardiac disorders linked to fibrotic tissue. Following diagnosis of pleural effusion or pulmonary fibrosis, the discontinuance of cabergoline has been reported to result in improvement of signs and symptoms.

Erythrocyte sedimentation rate (ESR) has been found to be abnormally increased in association with pleural effusion/fibrosis. Chest x-ray examination is recommended in cases of unexplained ESR increases to abnormal values. Serum creatinine measurements can also be used to help in the diagnosis of fibrotic disorder.
Psychiatric: Pathological gambling, increased libido, and hypersexuality have been reported in patients treated with dopamine agonists including cabergoline. This has been generally reversible upon reduction of the dose or treatment discontinuation (see **Post-marketing Surveillance data**).

Information for Patients
Patients should be instructed to notify their physician if they suspect they are pregnant, become pregnant, or intend to become pregnant during therapy. A pregnancy test should be done if there is any suspicion of pregnancy and continuation of treatment should be discussed with their physician.
A patient should notify their physician if they develop shortness of breath, persistent cough, difficulty with breathing when lying down, or swelling in their extremities.

Drug Interactions
Cabergoline should not be administered concurrently with D_2-antagonists, such as phenothiazines, butyrophenones, thioxanthenes, or metoclopramide.

Carcinogenesis and Mutagenesis and Impairment of Fertility
Carcinogenicity studies were conducted in mice and rats with cabergoline given by gavage at doses up to 0.98 mg/kg/day and 0.32 mg/kg/day, respectively. These doses are 7 times and 4 times the maximum recommended human dose calculated on a body surface area basis using total mg/m ^{2}/week in rodents and mg/m^2/week for a 50 kg human.
There was a slight increase in the incidence of cervical and uterine leiomyomas and uterine leiomyosarcomas in mice. In rats, there was a slight increase in malignant tumors of the cervix and uterus and interstitial cell adenomas. The occurrence of tumors in female rodents may be related to the prolonged suppression of prolactin secretion because prolactin is needed in rodents for the maintenance of the corpus luteum. In the absence of prolactin, the estrogen/progesterone ratio is increased, thereby increasing the risk for uterine tumors. In male rodents, the decrease in serum prolactin levels was associated with an increase in serum luteinizing hormone, which is thought to be a compensatory effect to maintain testicular steroid synthesis. Since these hormonal mechanisms are thought to be species-specific, the relevance of these tumors to humans is not known.
The mutagenic potential of cabergoline was evaluated and found to be negative in a battery of *in vitro* tests. These tests included the bacterial mutation (Ames) test with *Salmonella typhimurium*, the gene mutation assay with *Schizosaccharomyces pombe* P_1 and V79 Chinese hamster cells, DNA damage and repair in *Saccharomyces cerevisiae* D_4, and chromosomal aberrations in human lymphocytes. Cabergoline was also negative in the bone marrow micronucleus test in the mouse.
In female rats, a daily dose of 0.003 mg/kg for 2 weeks prior to mating and throughout the mating period inhibited conception. This dose represents approximately 1/28 the maximum recommended human dose calculated on a body surface area basis using total mg/m ^{2}/week in rats and mg/m^2/week for a 50 kg human.

Pregnancy: Teratogenic Effects: Category B
Reproduction studies have been performed with cabergoline in mice, rats, and rabbits administered by gavage.
(Multiples of the maximum recommended human dose in this section are calculated on a body surface area basis using total mg/m ^{2}/ week for animals and mg/m^2/week for a 50 kg human.)
There were maternotoxic effects but no teratogenic effects in mice given cabergoline at doses up to 8 mg/kg/day (approximately 55 times the maximum recommended human dose) during the period of organogenesis.
A dose of 0.012 mg/kg/day (approximately 1/7 the maximum recommended human dose) during the period of organogenesis in rats caused an increase in post-implantation embryofetal losses. These losses could be due to the prolactin inhibitory properties of cabergoline in rats. At daily doses of 0.5 mg/kg/day (approximately 19 times the maximum recommended human dose) during the period of organogenesis in the rabbit, cabergoline caused maternotoxicity characterized by a loss of body weight and decreased food consumption. Doses of 4 mg/kg/day (approximately 150 times the maximum recommended human dose) during the period of organogenesis in the rabbit caused an increased occurrence of various malformations. However, in another study in rabbits, no treatment-related malformations or embryofetotoxicity were observed at doses up to 8 mg/kg/day (approximately 300 times the maximum human dose).
In rats, doses higher than 0.003 mg/kg/day (approximately 1/28 the maximum recommended human dose) from 6 days before parturition and throughout the lactation period inhibited growth and caused death of offspring due to decreased milk secretion.
There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from cabergoline, a decision should be made whether to discontinue nursing

or to discontinue the drug, taking into account the importance of the drug to the mother. Use of cabergoline for the inhibition or suppression of physiologic lactation is not recommended (see **PRECAUTIONS section**).
The prolactin-lowering action of cabergoline suggests that it will interfere with lactation. Due to this interference with lactation, cabergoline should not be given to women postpartum who are breastfeeding or who are planning to breastfeed.

Pediatric Use
Safety and effectiveness of cabergoline in pediatric patients have not been established.

Geriatric Use
Clinical studies of cabergoline did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS
The safety of Cabergoline Tablets has been evaluated in more than 900 patients with hyperprolactinemic disorders. Most adverse events were mild or moderate in severity.
In a 4-week, double-blind, placebo-controlled study, treatment consisted of placebo or cabergoline at fixed doses of 0.125, 0.5, 0.75, or 1 mg twice weekly. Doses were halved during the first week. Since a possible dose-related effect was observed for nausea only, the four cabergoline treatment groups have been combined. The incidence of the most common adverse events during the placebo-controlled study is presented in the following table.
Incidence of Reported Adverse Events During the 4-week, Double-Blind, Placebo-Controlled Trial

Adverse Event*	Cabergoline (n = 168) 0.125 to 1 mg two times a week	Placebo (n = 20)
	Number (percent)	
Gastrointestinal		
Nausea	45 (27)	4 (20)
Constipation	16 (10)	0
Abdominal pain	9 (5)	1 (5)
Dyspepsia	4 (2)	0
Vomiting	4 (2)	0
Central and Peripheral Nervous System		
Headache	43 (26)	5 (25)
Dizziness	25 (15)	1 (5)
Paresthesia	2 (1)	0
Vertigo	2 (1)	0
Body As Hyperlink Whole		
Asthenia	15 (9)	2 (10)
Fatigue	12 (7)	0
Hot flashes	2 (1)	1 (5)
Psychiatric		
Somnolence	9 (5)	1 (5)
Depression	5 (3)	1 (5)
Nervousness	4 (2)	0
Autonomic Nervous System	6 (4)	0
Postural hypotension		
Reproductive - Female		
Breast pain	2 (1)	0
Dysmenorrhea	2 (1)	0
Vision Abnormal vision	2 (1)	0
*Reported at ≥1% for cabergoline		

In the 8-week, double-blind period of the comparative trial with bromocriptine, cabergoline (at a dose of 0.5 mg twice weekly) was discontinued because of an adverse event in 4 of 221 patients (2%) while bromocriptine (at a dose of 2.5 mg two times a day) was discontinued in 14 of 231 patients (6%). The most common reasons for discontinuation from cabergoline were headache, nausea and vomiting (3, 2, and 2 patients, respectively); the most common reasons for discontinuation from bromocriptine were nausea, vomiting, headache, and dizziness or vertigo (10, 3, 3, and 3 patients, respectively). The incidence of the most common adverse events during the double-blind portion of the comparative trial with bromocriptine is presented in the following table.

Incidence of Reported Adverse Events During the 8-week, Double-Blind Period of the Comparative Trial With Bromocriptine Title Here

	Cabergoline	Bromocriptine
Adverse Event*	(n = 221)	(n = 231)
	Number (percent)	
Gastrointestinal		
Nausea	63 (29)	100 (43)
Constipation	15 (7)	21 (9)
Abdominal pain	12 (5)	19 (8)
Dyspepsia	11 (5)	16 (7)
Vomiting	9 (4)	16 (7)
Dry mouth	5 (2)	2 (1)
Diarrhea	4 (2)	7 (3)
Flatulence	4 (2)	3 (1)
Throat irritation	2 (1)	0
Toothache	2 (1)	0
Central and Peripheral Nervous System		
Headache	58 (26)	62 (27)
Dizziness	38 (17)	42 (18)
Vertigo	9 (4)	10 (4)
Paresthesia	5 (2)	6 (3)
Body As Hyperlink Whole		
Asthenia	13 (6)	15 (6)
Fatigue	10 (5)	18 (8)
Syncope	3 (1)	3 (1)
Influenza-like symptoms	2 (1)	0
Malaise	2 (1)	0
Periorbital edema	2 (1)	2 (1)
Peripheral edema	2 (1)	1
Psychiatric		
Depression	7 (3)	5 (2)
Somnolence	5 (2)	5 (2)
Anorexia	3 (1)	3 (1)
Anxiety	3 (1)	3 (1)
Insomnia	3 (1)	2 (1)
Impaired concentration	2 (1)	1
Nervousness	2 (1)	5 (2)
Cardiovascular		
Hot flashes	6 (3)	3 (1)
Hypotension	3 (1)	4 (2)
Dependent edema	2 (1)	1
Palpitation	2 (1)	5 (2)
Reproductive - Female		

Breast pain	5 (2)	8 (3)
Dysmenorrhea	2 (1)	1
Skin and Appendages		
Acne	3 (1)	0
Pruritus	2 (1)	1
Musculoskeletal		
Pain	4 (2)	6 (3)
Arthralgia	2 (1)	0
Respiratory Rhinitis	2 (1)	9 (4)
Vision Abnormal vision	2 (1)	2 (1)
*Reported at ≥1% for cabergoline		

Other adverse events that were reported at an incidence of <1.0% in the overall clinical studies follow.
Body as a Whole: facial edema, influenza-like symptoms, malaise
Cardiovascular System: hypotension, syncope, palpitations
Digestive System: dry mouth, flatulence, diarrhea, anorexia
Metabolic and Nutritional System: weight loss, weight gain
Nervous System: somnolence, nervousness, paresthesia, insomnia, anxiety
Respiratory System: nasal stuffiness, epistaxis
Skin and Appendages: acne, pruritus
Special Senses: abnormal vision
Urogenital System: dysmenorrhea, increased libido
The safety of cabergoline has been evaluated in approximately 1,200 patients with Parkinson's disease in controlled and uncontrolled studies at dosages of up to 11.5 mg/day which greatly exceeds the maximum recommended dosage of cabergoline for hyperprolactinemic disorders. In addition to the adverse events that occurred in the patients with hyperprolactinemic disorders, the most common adverse events in patients with Parkinson's disease were dyskinesia, hallucinations, confusion, and peripheral edema. Heart failure, pleural effusion, pulmonary fibrosis, and gastric or duodenal ulcer occurred rarely. One case of constrictive pericarditis has been reported.
Post-marketing Surveillance data: The following events have been reported in association with cabergoline: valvulopathy and fibrosis, (see **WARNINGS, Valvulopathy and PRECAUTIONS, Fibrosis**).
Others events have been reported in association with cabergoline: hypersexuality, increased libido, pathological gambling (see **PRECAUTIONS, Psychiatric**). In addition, during post-marketing surveillance, cases of alopecia, aggression and psychotic disorder have been reported in patients taking Cabergoline. Some of these reports have been in patients who have had prior adverse reactions to dopamine agonist products.

OVERDOSAGE

Overdosage might be expected to produce nasal congestion, syncope, or hallucinations. Measures to support blood pressure should be taken if necessary.

DOSAGE AND ADMINISTRATION

The recommended dosage of Cabergoline Tablets for initiation of therapy is 0.25 mg twice a week. Dosage may be increased by 0.25 mg twice weekly up to a dosage of 1 mg twice a week according to the patient's serum prolactin level. Before initiating treatment, cardiovascular evaluation should be performed and echocardiography should be considered to assess for valvular disease.
Dosage increases should not occur more rapidly than every 4 weeks, so that the physician can assess the patient's response to each dosage level. If the patient does not respond adequately, and no additional benefit is observed with higher doses, the lowest dose that achieved maximal response should be used and other therapeutic approaches considered. Patients receiving long term treatment with Cabergoline should undergo periodic assessment of their cardiac status and echocardiography should be considered.
After a normal serum prolactin level has been maintained for 6 months, cabergoline may be discontinued, with periodic monitoring of the serum prolactin level to determine whether or when treatment with cabergoline should be reinstituted. The durability of efficacy beyond 24 months of therapy with cabergoline has not been established.

HOW SUPPLIED

Cabergoline Tablets are a white to off-white, oval shape, flat face, beveled edge tablet containing 0.5 mg cabergoline. Each tablet is debossed "P" bisect line "P" on one side and "673" on the other side.
Cabergoline Tablets are available as follows:

Bottles of 8 tablets	NDC 49884-673-14

Storage
Store at controlled room temperature 20° to 25° C (68° to 77° F) [see USP].
Manufactured by:
PAR PHARMACEUTICAL COMPANIES, INC.
Spring Valley, NY 10977

Issued: R 04/08 OS673-14-1-03

PRINCIPAL DISPLAY PANEL 0.5 MG TABLETS